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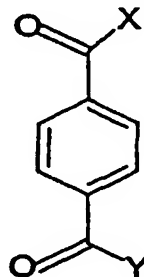
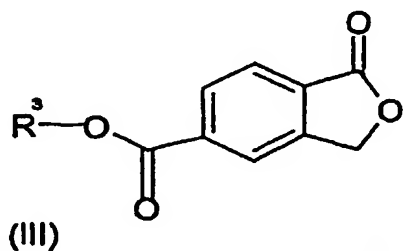
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(54) Title: INTERMEDIATES FOR THE PREPARATION OF CITALOPRAM AND ESCITALOPRAM



(VIIIa)

(57) Abstract: Methods for manufacture of 5-alkoxycarbonylphthalides are disclosed. The 5-alkoxycarbonylphthalides are useful in syntheses of the well-known antidepressants citalopram and escitalopram. A method for preparing an alkoxycarbonylphthalide of formula (III) comprising: (a) reacting a compound of formula (VIIIa) with a formaldehyde and oleum; and (b) addition of an alcohol R<sup>3</sup>-OH to the reaction of step (a); wherein X and Y of formula (VIIIa) may be selected independently from the group consisting of: OR<sup>1</sup>, OR<sup>2</sup>, a halogen (such as Cl, Br, I), and NR; wherein R, R<sup>1</sup> and R<sup>2</sup> are independently h or a C<sub>1-6</sub> alkyl or phenyl.

# INTERNATIO SEARCH REPORT

In: Application No  
PCT/DK2004/000177

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D307/88

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 118 614 A (NORPHARMA SPA) 25 July 2001 (2001-07-25) cited in the application column 2 - column 4; examples	1-49
Y	WO 01/32642 A (DAHLBERG NIELSEN POUL ;PETERSEN HANS (DK); LUNDBECK & CO AS H (DK)) 10 May 2001 (2001-05-10) cited in the application page 2	1-49
Y	WO 00/39112 A (DAHLBERG NIELSEN POUL ;PETERSEN HANS (DK); LUNDBECK & CO AS H (DK)) 6 July 2000 (2000-07-06) cited in the application	1-49
X	page 5, line 26; example 1 ----- -/-	50-58

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- \*&\* document member of the same patent family

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Ir Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/19513 A (PETERSEN HANS ;LUNDBECK & CO AS H (DK)) 14 May 1998 (1998-05-14) cited in the application	1-49
X	page 7; examples 1,2 -----	50-58
X	ANZALONE ET AL.: "Substituent Effects on Hydrogenation of Aromatic Rings: Hydrogenation vs. Hydrogenolysis in Cyclic Analogues of Benzyl Ethers" J. ORG. CHEM., vol. 50, 1985, pages 2128-2133, XP002282189 cited in the application page 2129; example 22 -----	50-58
X	SUGIMORI, AKIRA ET AL: "Radiation-induced reduction of aromatic carboxylic esters in alcoholic solutions" CHEMISTRY LETTERS (1980), (5), 483-6, 1980, XP001189503 cited in the application page 484; example 6 -----	50-58
X	LEROY S FORNEY: "REACTION OF TEREPHTHALIC ACID WITH FORMALDEHYDE IN SULFUR TRIOXIDE MEDIA" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 35, no. 5, May 1970 (1970-05), pages 1695-1696, XP002936415 ISSN: 0022-3263 cited in the application page 1696 -----	50-58

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK2004/000177

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-49

Claim 1 and dependent upon relate to a method for preparing an alkoxycarbonylphtalide of formula (III), comprising reacting a compound of formula (VIIIa) with a formaldehyde and oleum and then adding an alcohol of formula R3OH.

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2. claims: 50-56

Claim 50 and dependent upon disclose a method for preparing an intermediate suitable for the synthesis of citalopram or escitalopram, comprising the steps of preparing a compound of formula (III) and then isolating it.

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3. claims: 57-58

Claims 57 and 58 relate to compounds of formula (III).

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PCT/DK2004/000177

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Information on patent family members

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